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Definitions and Clinical Trial Design Principles for Coronary Artery Chronic Total Occlusion Therapies

CTO-ARC Consensus Recommendations

ABSTRACT: Over the past 2 decades, chronic total occlusion (CTO) percutaneous coronary intervention has developed into its own subspecialty of interventional cardiology. Dedicated terminology, techniques, devices, courses, and training programs have enabled progressive advancements. However, only a few randomized trials have been performed to evaluate the safety and efficacy of CTO percutaneous coronary intervention. Moreover, several published observational studies have shown conflicting data. Part of the paucity of clinical data stems from the fact that prior studies have been suboptimally designed and performed. The absence of standardized end points and the discrepancy in definitions also prevent consistency and uniform interpretability of reported results in CTO intervention. To standardize the field, we therefore assembled a broad consortium comprising academicians, practicing physicians, researchers, medical society representatives, and regulators (US Food and Drug Administration) to develop methods, end points, biomarkers, parameters, data, materials, processes, procedures, evaluations, tools, and techniques for CTO interventions. This article summarizes the effort and is organized into 3 sections: key elements and procedural definitions, end point definitions, and clinical trial design principles. The Chronic Total Occlusion Academic Research Consortium is a first step toward improved comparability and interpretability of study results, supplying an increasingly growing body of CTO percutaneous coronary intervention evidence.

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Marked improvements in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) technology and techniques have been realized in the past 2 decades. However, only a few randomized trials have been performed to evaluate the safety and efficacy of CTO-PCI. Unique considerations are required to properly evaluate CTO therapies, including selection of the appropriate study population, control group, background medications, procedures, effectiveness and safety end points, and learning curve issues. In this regard, standardized end points and definitions would provide consistency and uniform interpretability of reported results of CTO intervention.[1]

The coronary Chronic Total Occlusion Academic Research Consortium (CTO-ARC) was assembled to develop procedural and end point definitions for clinical studies of CTO-PCI that can be used in clinical registries, trials, and device investigations and to recommend design principles for clinical trials and registries investigating

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The full author list is available on page 495.

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CTO therapies. Toward this end, an in-person meeting was held in November 2018 attended by stakeholders and experts in CTO-PCI from North America and Europe (Data Supplement). Representatives from the US Food and Drug Administration participated in an advisory role. CTO-ARC was funded by multiple industry sponsors that did not actively participate in either the session or document preparation but were permitted to attend the discussions and were provided a copy of the report at the time of submission. No fees or honoraria were provided to the writing group or participants, but travel expenses were reimbursed.

This article summarizes the current state of knowledge and consensus expert opinion for CTO-PCI and is organized into 3 sections: end point definitions, clinical trial design principles, and key elements and procedural definitions. Because the field of CTO-PCI is highly dynamic and evolving, we anticipate subsequent revisions to these recommendations.

KEY ANATOMIC AND PROCEDURAL DEFINITIONS

Definition of a CTO

A variety of definitions have been used to define a CTO (Table I in the Data Supplement). The 2 key characteristics of a CTO are an occlusion with absence of antegrade flow through the lesion with a presumed or documented duration of ≥3 months. CTOs must have absent antegrade flow through the lesion (TIMI [Thrombolysis in Myocardial Infarction] grade 0 flow). Bridging collaterals may antegradely fill the target vessel as long as there is absence of antegrade flow through the lesion. Functional occlusions, defined as those with TIMI grade 1 antegrade flow through a severely stenosed but patent lumen, even if not visible on angiography, do not qualify as CTOs. In addition to TIMI grade 0 flow, the typical appearance of a CTO includes angiographically visible mature collaterals and the absence of thrombus or staining at the proximal cap. Because classifying a lesion as a CTO may be challenging, a core laboratory with CTO expertise is recommended to verify that lesions enrolled in CTO studies are indeed CTOs (and to otherwise characterize CTO features).

Because occlusions <3 months in age are likely to have higher rates of acute procedural success compared with older lesions, knowing the occlusion duration is desirable. However, definitive occlusion duration information (eg, prior angiogram demonstrating a total occlusion or acute myocardial infarction [MI] that is left untreated) is uncommon.

CTO-ARC proposes that CTOs should be classified as definite and probable CTOs, as described in Table 1. Studies can then report the proportion of each type of CTO and the method used to corroborate the occlusion duration.

Table 1. CTO Criteria: Definite Versus Probable

CTO criteria	Definition
Definite CTO	CTO with typical appearance* and definitive corroborating evidence of occlusion duration ≥3 mo
Probable CTO	CTO with typical appearance*

CTO indicates coronary chronic total occlusion.
*Thrombolysis in Myocardial Infarction grade 0 flow through the lesion with no thrombus, no staining at the proximal cap, and presence of mature collaterals.

Vessel Architecture

A modern approach to CTO-PCI involves embracing the concept of vessel architecture, which is the vascular space contained by the naturally resistant adventitia, including the occlusive plaque and vessel wall (Figure).[2] Normal coronary arteries consist of intimal, medial, and adventitial layers. However, identifying the 3-layer structure of the vessel wall may be challenging in a chronically occluded vessel even by intravascular imaging because of extensive architectural disruption. For practical purposes, it is most useful to distinguish between the occlusive plaque (composed of the former true lumen now occupied by atherosclerotic plaque and organized thrombus) and what lies outside it (media and adventitia). Plaque or atherosclerosis is a disease of the intima that is bounded by the internal elastic lamina. CTO-ARC therefore recommends using the nomenclature intraplaque (for wire tracking within the occlusive intima-based plaque) and extraplaque (for wire tracking outside the plaque but still contained within the adventitial layer) in future studies when describing the device course within the occluded CTO segment. With this perspective, the imprecise terms "subintimal," "subadventitial," "intramural," "extramural," "true lumen," and "false lumen," which are commonly used in the CTO literature in descriptions of the suspected position of devices, wires, and stents within the CTO segment, can be abandoned. An exception to this rule is that the terms "true lumen" and "false lumen" can still be used in the specific situation of the segments proximal and distal to the CTO caps, wherein a wire or a dedicated dissection device may track within the artery wall rather than within the true lumen (such as in the "scratch and go" technique or when a device is used to reenter into the true lumen).

Intravascular ultrasound studies have shown that the wire course within CTOs is not always completely intraplaque or extraplaque[3]; intraplaque tracking can be detected in >10% of cases when dissection/reentry techniques are used, and extraplaque tracking can be observed in >25% of cases where a true-to-true lumen approach is reported.[4,5] CTO-ARC therefore

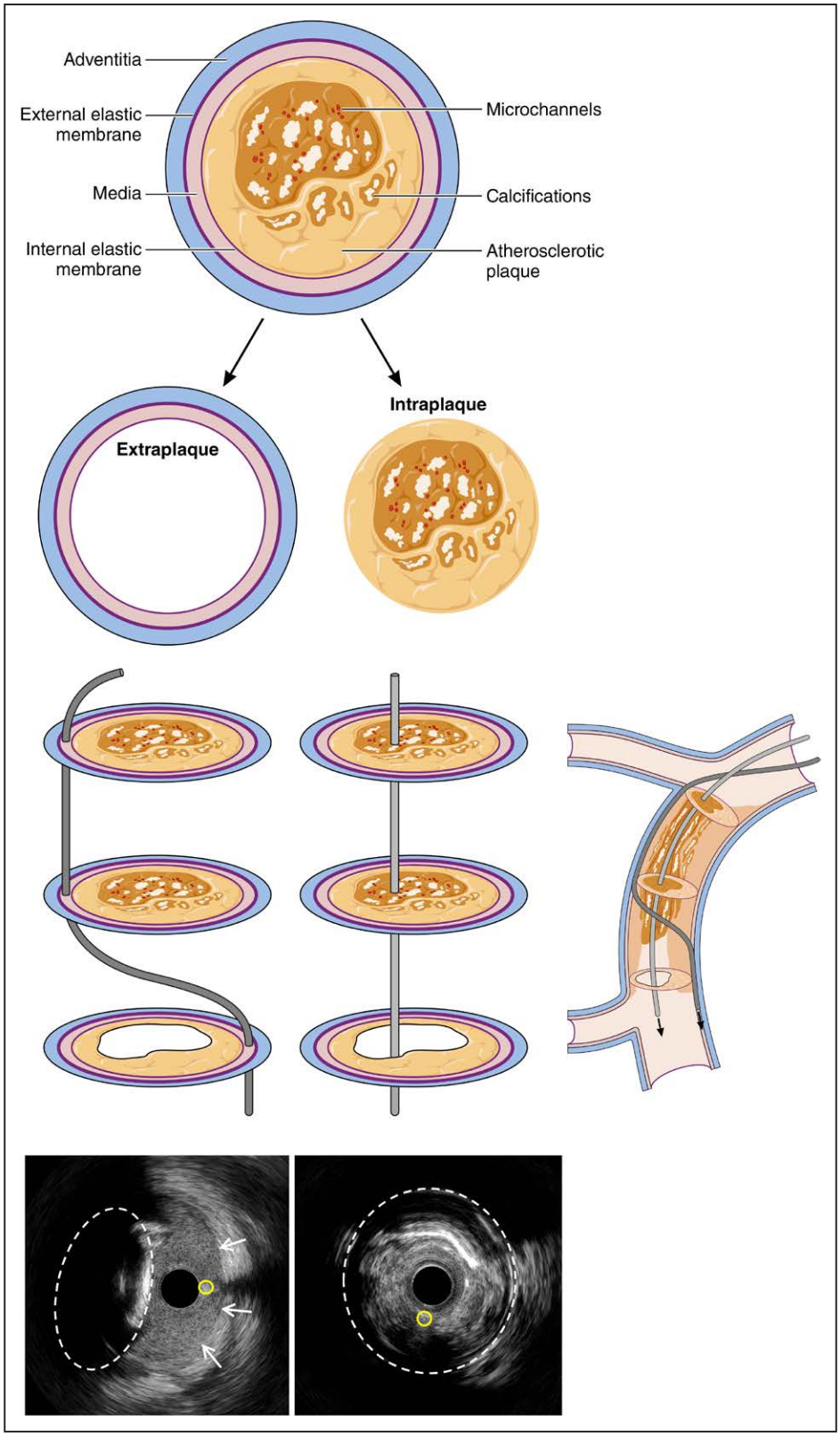

Figure. Vessel architecture: intraplaque and extraplaque structures.
Intravascular ultrasound images. White dotted circles indicate plaque; yellow circles indicate the guide wire; and white arrows show a monolayer appearance of the vessel, indicating absence of the intimal layer.

recommends that intravascular imaging studies describe device positioning as intraplaque versus extraplaque and that intraplaque versus extraplaque track length be reported when possible. Future studies are needed to evaluate the use of specific cutoffs to define extraplaque tracking (eg, >10 mm, >50% of occlusion

length) and to determine the clinical implications of its occurrence.

Lesion Crossing Strategies

CTO strategies can be divided into the antegrade approach (approaching the occlusion segment from the proximal CTO cap with the intention of crossing the distal CTO cap into the distal true lumen) and the retrograde approach (approaching the occlusion segment from the distal CTO cap with the intention of accessing the proximal CTO cap into true lumen). In addition, strategies can be described according to the technique used: wiring versus dissection-reentry (Table 2). As previously discussed, discordance has consistently been demonstrated between the intended crossing technique and the precise guide wire course.[4,5] Therefore, CTO-ARC recommends reporting the intended wiring technique to traverse the CTO segment, whether through the plaque (intraplaque) or around the plaque (extraplaque), regardless of the actual position of the wire. In studies that attempt to evaluate the relative risks or benefits of techniques according to the equipment position inside the vessel, intravascular imaging is needed to determine whether the strategy used was intraplaque (wholly or in part) or extraplaque.

The strategy nomenclature ideally captures all the nuances and techniques used during a procedure, defines which strategy was the successful one, and is simple and concise enough to be applied in studies. The successful strategy is defined as the one that connects the proximal luminal segment of the CTO to its distal counterpart. Studies have reported an increased risk of complications with the retrograde approach, although some complications resulted from the antegrade component of the procedure (eg, a failed retrograde attempt followed by an antegrade wiring strategy leading to perforation or a failed antegrade attempt associated with perforation that was successfully treated with retrograde bailout).[6] To avoid future uncertainty and misclassification, CTO-ARC recommends that CTO-PCI registries and trials use the following strategy nomenclature to define the successful strategy of a particular case: "antegrade wiring," "antegrade dissection-reentry," "retrograde wiring," and "retrograde dissection-reentry" (Table 2). When antegrade techniques are used (antegrade wiring or antegrade dissection-reentry), if any attempt was made to cross a retrograde channel (whether successfully or not), the suffix "R" should be added (eg, AW-R); otherwise, the suffix "0" should be notated for no retrograde attempt. If a complication occurs, it is important to determine the strategy that caused the complication (defined as the last strategy used before the fluoroscopy or cine run that documented the complication). Complications that occurred with antegrade preparation during a retrograde approach or any proximal vessel manipulation during reverse controlled antegrade and retrograde tracking technique are considered part of the retrograde approach.[6]

Table 2. Classification of CTO Strategies

Approach and crossing technique	Definition	Retrograde approach contribution
AW	Wire-based technique with the intention of traversing from the proximal vessel true lumen through the CTO to the distal vessel true lumen	No: AW-0 Yes: AW-R
ADR	Dissection technique (wire based or device based with a dedicated dissection device or equivalent) with the intention of passing from the proximal vessel lumen through a dissection plane followed by reentry into the distal vessel lumen at or beyond the distal cap of the occlusion	No: ADR-0 Yes: ADR-R
RW	Wire-based technique with the intention of traversing from the distal vessel true lumen to the proximal vessel true lumen	…
RDR	Dissection technique (usually with knuckled wires) with the intention of connecting an antegrade dissection plane and a retrograde dissection plane, with wires advanced antegrade and/or retrograde	…

ADR indicates antegrade dissection and reentry; AW, antegrade wiring; CTO, coronary chronic total occlusion; R, retrograde attempt; RDR, retrograde dissection and reentry; RW, retrograde wiring; and 0, no retrograde attempt.

Antegrade wire escalation remains the most commonly used technique in CTO-PCI. This term supposes an escalation of stiffness of the wires used during the procedure. However, many antegrade wiring procedures involve only 1 wire; some will involve deescalation of wire stiffness after a proximal cap puncture to travel within the CTO segment followed by reescalation of the stiffness; and some may even involve only deescalation. In view of these considerations, CTO-ARC recommends the use of the term antegrade wiring, without assumption of escalation.

Reentry can be performed with dedicated devices or with only wires, straight or knuckled. Many forms of wire-based dissection-reentry techniques have been described. Less controlled techniques include antegrade fenestration and reentry. Uncontrolled techniques include subintimal tracking and reentry, contrast-guided subintimal tracking and reentry, mini–subintimal tracking and reentry, and limited antegrade subintimal tracking (Table II in the Data Supplement). To avoid misclassification, we recommend using the general term "wire-based reentry" when no dedicated device for reentry was used or device-based reentry otherwise, with no need to describe the specific method used.

Retrograde wiring and retrograde dissection-reentry definitions are described in Table 2. CTO-ARC recognizes the controversy with regard to labeling all controlled antegrade and retrograde tracking technique or reverse-controlled antegrade and retrograde tracking technique as dissection-reentry techniques because some maneuvers may be performed exclusively intraplaque, especially when performed with straight wires and smaller balloons. However, given the potential misclassification and the high prevalence of extraplaque tracking even with straight wires, the more general term retrograde dissection-reentry is recommended.

The subcategories of the antegrade and retrograde approaches described in Table 2 should be adopted to allow further clarification of the effectiveness and safety of each strategy. Although current data suggest increased complication rates with the retrograde approach, the extent to which this is the result of selection bias is unclear because retrograde procedures are more likely used in increasingly complex lesions.[6–8] To identify the safety and efficacy of each specific strategy or combination of strategies, CTO-ARC recommends documenting each strategy used in order, with clear notation as to when successful wire crossing was achieved and when any complications arose.

Vessel and Lesion Characteristics

The vessel and lesion characteristics that reflect CTO complexity and that are essential elements in PCI success prediction models are CTO length, cap morphology, lesion calcification, intralesion angulation, and proximal vessel tortuosity. For further details, see the Vessel and Lesion Characteristics section and Figure I in the Data Supplement.[9–12]

CTO Devices and Equipment

Although guide wires possess many features, 3 are most relevant for CTO intervention: tip load, tip taper, and the presence of a polymer jacket versus exposed coils. Microcatheters can be broadly classified by torque and profile. For further details, see the CTO Devices and Equipment section and Table III in the Data Supplement.[13]

Collateral Channels

Collaterals are defined as interarterial connections that provide blood flow to a vascular territory in which the original supply vessel is obstructed. Collateral vessels are categorized as contralateral versus ipsilateral, bridging collaterals, and septal or nonseptal.[6,13–22] CTO-ARC recommends that studies evaluating the feasibility of the retrograde approach or risk assessment of collaterals should use the Werner and McEntegart classifications to appropriately discriminate the type of collaterals analyzed. For further details, see the Collateral Channels section and Tables IV and V in the Data Supplement.

Complexity Scores

CTO-ARC recommends the collection of all variables considered in the J-CTO (Multicentre CTO Registry in Japan), PROGRESS-CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention), RECHARGE (Registry of CrossBoss and Hybrid Procedures in France, the Netherlands, Belgium and United Kingdom), and CASTLE (EuroCTO) scores, with special attention to exact definitions. These features are best assessed under dual catheter injection when contralateral collaterals are present. This allows characterization of the CTO population according to the most widely used scores and will facilitate comparison with previous studies while preserving applicability for new developments.[9,11,12,23,24] For further details, see the Complexity Scores Definitions section and Tables VI and VII in the Data Supplement.

DEFINITIONS OF EFFICACY END POINTS

Crossing, Technical, Device, and Procedural Success

Interpretation and comparison of CTO trials have been challenged by variability in study design and inconsistencies in procedural and clinical end point definitions. In many such studies, lack of systematic biomarker assessment and absence of independent monitoring and event adjudication likely contributed to event rate underreporting and inaccuracy, further limiting the generalizability of their results.[20,25] As a result, rates of procedural success among contemporary CTO trials range from ≈70% to >90%, and in-hospital major adverse events vary from 0.5% to nearly 20%.[26,27] Thus, a need remains to standardize procedural, device-related, and patient-oriented outcomes across clinical and regulatory CTO trials. Uniformity in end point definitions permits a basis for comparison of outcomes across studies of different design. To establish common end points specific to CTO-PCI, the following definitions are recommended.

Crossing Success

This end point is defined as angiographic or intravascular imaging confirmation of guide wire (or related device) placement in the true lumen of the main vessel beyond the occluded segment. Guide wire placement into the distal true lumen (if from the antegrade direction) or in the proximal true lumen (if from the retrograde direction) is considered a CTO crossing success.

Guide wire placement at the distal cap of a CTO from a retrograde direction through a collateral is defined as

collateral crossing success but is not considered crossing success until the wire is successfully passed into the true lumen proximal to the CTO.

Technical Success

Technical success is defined as achievement of TIMI grade 2 or greater antegrade flow in all ≥2.5-mm distal branches with <30% residual stenosis of the target CTO lesion at procedure end, ideally assessed by quantitative coronary angiography by an independent core laboratory. Previous studies have sometimes called this angiographic success. Although it is recognized that TIMI grade 2 flow may confer a more adverse prognosis in specific type of procedures such as subintimal tracking and reentry, it is often difficult to achieve TIMI grade 3 flow given competitive collateral flow is present. Partial technical success is defined as achievement of TIMI grade 2 or greater antegrade flow with <30% residual stenosis into at least 1 but not all ≥2.5-mm distal side branches. CTO-ARC recommends documenting the final residual stenosis and TIMI flow in all branch vessels (ideally by an angiographic core laboratory to remove intersite variability).

Device Success

Device success describes performance attributed to a specific study device. According to the type of study, device success may be equivalent to crossing success (eg, for studies comparing different guide wires or crossing devices) or technical success (eg, for studies comparing different stents). In some studies, both CTO crossing and stent-related outcomes are evaluated.

Procedural Success

Similar to other non-CTO trials, procedural success is defined as technical success plus the absence of an in-hospital major adverse cardiovascular event (MACE; death, MI, or clinically driven target vessel revascularization [TVR]). Procedural success may be subclassified as complete or partial, depending on whether technical success was complete or partial.

Health-Related Outcomes

The primary goal of CTO revascularization is to alleviate symptoms and functional limitations and to optimize quality of life (QOL).[28,29] The optimal assessment of these symptoms is therefore of paramount importance in defining the benefits of revascularization. However, a substantial proportion of patients present with atypical angina or angina-equivalent symptoms (eg, dyspnea on exertion).[30] Nonetheless, practical patient-reported assessment scales are available to characterize patient QOL. For example, the Seattle Angina Questionnaire (SAQ) includes 5 domains that evaluate not only angina frequency but also angina stability, physical limitation, treatment satisfaction, and QOL.[31] The SAQ has been strongly correlated with all-cause death, MI, and rehospitalization with acute coronary syndrome[28] and is accepted by the US Food and Drug Administration as a validated instrument to assess change in patient health status with interventions in clinical trials. Newer approaches to assess health outcomes, including activity level monitoring with electronic wearable devices, are under evaluation.

CTO-ARC endorses the recommendations proposed by Academic Research Consortium-2 (ARC-2) on health-related outcomes. A relevant consideration is to ascertain the extent to which exercise limitation contributes to patient reporting of minimal or no symptoms (the patient may not even be aware of the presence of symptoms). It is recommended that health-related QOL questionnaires be administered before CTO-PCI (and before randomization if applicable) and at ≥1 clinically relevant follow-up intervals, enabling measurement of absolute and relative changes in health status. Comprehensive assessment of health status outcomes is an important element for all CTO clinical trial designs, the principles of which are discussed in the Design Types and End Points for CTO Trials section.

DEFINITIONS OF SAFETY END POINTS

Death

The CTO-ARC consensus recommends that death in CTO studies be classified according to the ARC-2 criteria (Table VIII in the Data Supplement).[32]

Stroke

Although uncommon during CTO-PCI, stroke is a critical procedural complication of coronary revascularization procedures. CTO-ARC recommends the use of Neuro-ARC classification (Table IX in the Data Supplement).[33]

Nonprocedural MI

CTO-ARC endorses a modified the ARC-2 definition of nonprocedural MI, which was based on the 2012 third universal definition of myocardial infarction.[34] In 2018, the updated fourth universal definition was introduced, which largely maintained the prior thresholds and clinical criteria for spontaneous MI (requiring the use of cardiac troponin [cTn]) but added categorization of different causes of nonperiprocedural MI.[35] Therefore, CTO-ARC further endorses the fourth universal definition for nonprocedural MI (Table X in the Data Supplement).

Procedural MI

Numerous definitions of procedural (type 4a) MI are currently in widespread use, including those from the fourth universal definition, the Society for

Cardiovascular Angiography & Interventions (SCAI) definition of a clinically relevant MI, and the ARC-2 definition.[32,35,36] Rates of procedural MI may vary widely with the use of these differing definitions, which may affect clinical trial event rates and makes interstudy comparison difficult. Because all of these definitions are biomarker based (with or without supporting evidence of myocardial ischemia), CTO-ARC favors use of a procedural MI definition that has been demonstrated to be prognostically important and that minimizes ascertainment bias between different procedure types.

The most recent (fourth) universal definition of MI for peri-PCI (type 4a) MI requires a cTn elevation >5 times the 99th percentile of the upper reference limit (URL) within 48 hours after the procedure in patients with normal baseline values plus the presence of additional supportive electrocardiographic, angiographic, or imaging evidence of ischemia. Different criteria are used if the baseline cTn level is elevated but stable or falling. No criteria are provided if the baseline cTn level is elevated and rising (or not known to have peaked). Moreover, despite acknowledging the wider dynamic range of high-sensitivity (hs)-cTn assays, the 5-times threshold is also adopted for these assays. The development of new pathological Q waves and autopsy evidence of recent procedure-related thrombus in the culprit artery also meet the definition of type 4a MI, regardless of cTn values. A peri–coronary artery bypass graft (CABG; type 5) MI is defined as a cTn (or hs-cTn) elevation >10 times the 99th percentile of the URL within 48 hours after the procedure in patients with normal baseline values (the higher threshold after CABG compared with PCI being arbitrary) with supportive electrocardiographic, angiographic, or imaging evidence of ischemia, although these criteria also differ from those after PCI.

In contrast with the universal definition, the SCAI expert consensus committee selected a definition for periprocedural biomarker elevation that was shown in multiple studies to be independently associated with subsequent mortality after controlling for baseline clinical and angiographic covariates. In this regard, a distinction was drawn between nonprocedural MIs, for which even small elevations of cTn predict subsequent death, and procedural MIs, for which most studies have found that only large biomarker elevations (eg, peak creatine kinase-MB [CK-MB] ≥10 times URL, representing extensive myonecrosis) are correlated with cardiovascular or all-cause death after PCI.[37–40] Of note, whereas the fourth universal definition requires troponin to assess MI, the SCAI definition prefers CK-MB as its biomarker of choice for periprocedural MI assessment because its relationship with subsequent death is stronger than with troponins.[37–40] However, acknowledging that CK-MB levels are no longer routinely available in many hospitals, a standard cTn (I or T) rise to ≥70 times the URL meets post-PCI MI criteria, according to a 7:1 cTn:CK-MB ratio reported in series that measured both or assessed detectable infarcts by cardiac magnetic resonance imaging. For patients in whom new pathological Q waves develop, a ≥5 times CK-MB rise (or ≥35 times cTn elevation rise) also meets criteria for post-PCI MI by the SCAI definition. Last, on the basis of evidence supporting similar prognostic implications of 5 times and 10 times CK-MB elevations after PCI and CABG, the same thresholds were adopted for the definition of post-CABG MI without the requirement for supportive evidence of myocardial ischemia, thereby minimizing ascertainment bias between the procedures. Additional criteria are provided for patients with elevated biomarkers at baseline, depending on their trajectory (rising, falling or unknown). Several large-scale studies performed in the aftermath of the SCAI publication have validated these criteria.[41–44]

Acknowledging the desirability of a clinically relevant MI definition that minimizes PCI and CABG ascertainment bias but also recognizing the expanding availability of cTn assays, and in the spirit of compromise, the ARC-2 group defined procedural MI after both PCI and CABG as a cTn (or hs-cTn) elevation within 48 hours of ≥35 times URL plus new significant Q waves, flow-limiting angiographic complications, or new substantial loss of myocardium on imaging. An absolute rise in cTn to ≥70 times URL with or without other supportive findings was defined as significant periprocedural myocardial injury. The SCAI conventions were adopted for patients with elevated biomarkers at baseline.

Given the greater extent of atherosclerosis, procedural complexity, arterial injury, and stent length implantation required for CTO-PCI compared with non–CTO-PCI, the risk of procedural MI may be greater after CTO-PCI; it should not be assumed that the same threshold of clinical relevance applies for both conditions. Nine studies have examined the relationship of biomarker elevation after CTO-PCI and subsequent prognosis (Table XI in the Data Supplement). In the largest such study of 3712 consecutive patients undergoing PCI of at least 1 CTO lesion, a ≥18-fold increase in cTn T (which occurred in 20% of patients) was an independent predictor of median 2-year all-cause mortality.[45] This relationship held after both the antegrade and retrograde approach and was independent of procedural success or failure. In contrast, among 1058 consecutive successful CTO-PCI procedures, only a CK-MB rise >10 times URL was independently associated with subsequent morality at median 4.4-year follow-up.[46] The frequencies of procedural CK-MB elevations >3 times URL and >10 times URL were 11.8% and 2.8% respectively, demonstrating the varying sensitivity of the rate of procedural MI according to the definition selected. Similarly, among 639 patients undergoing CTO-PCI procedures, a post-PCI cTn elevation ≥70 times URL was associated with higher 1-year mortality, whereas lower

biomarker elevations were not.[42] In 6 other studies, lower level biomarker elevations after PCI had conflicting correlation with subsequent outcomes.[47–52] Thus, additional studies are required to determine whether the threshold for a clinically relevant periprocedural MI should be different after CTO-PCI and non–CTO-PCI.

Given the current weight of evidence, specifically the additional data supporting the independent relationship between only large postprocedural biomarker elevations and mortality published after the SCAI consensus document,[41–44] CTO-ARC recommends adoption of the SCAI definition of a clinically relevant MI after CTO-PCI and CABG procedures with use of either CK-MB or standard cTn biomarkers (Table 3). The use of hs-cTn assays is discouraged for this purpose given the current paucity of evidence relating hs-troponin threshold elevations to subsequent outcomes. In this regard, the use of hs-troponins may greatly inflate the absolute rate of procedural MI given that the upper bound of the URL of such assays is substantially (≥10-fold) lower than that for regular troponins. If hs-troponins must be used, CTO-ARC recommends the SCAI threshold of ≥70 times the 99th percentile of the URL for that hs-troponin assay plus the presence of at least 1 of the following criteria: (1) TIMI grade 0 to 1 flow in a main epicardial vessel or a side branch >2.0 mm in diameter that had TIMI grade 2 to 3 flow before PCI, (2) new pathological Q waves in ≥2 contiguous leads or new persistent left bundle-branch block, or (3) a new wall motion abnormality related to the procedure (Table 3). Last, given the availability of dozens of assays, each with their own specific URL, CTO-ARC recommends that for major trials a central biomarker core laboratory should use a uniform assay (either CK-MB or a standard [non-hs] troponin) to minimize intercenter variability and imprecision.

CTO-ARC recommends that in clinical trials cardiac biomarkers should be systematically measured before and after the procedure (timing is assay specific, generally beginning 3–6 hours after PCI, with ideally at least 2 postprocedure samples measured 8 hours apart; if values are elevated, additional draws should be collected until the peak has been reached). It is important to also obtain an ECG at baseline and within 24 hours after the procedure. The failure to assess ECGs and biomarkers may result in event underreporting and introduce bias. Adjudication by an independent Clinical Events Committee is recommended, especially when a procedural MI definition is used that includes clinical, angiographic or imaging information in addition to biomarkers. Last, CTO-ARC acknowledges that further studies are required specifically in the setting of CTO-PCI and CABG to establish the optimal biomarker and its thresholds for procedural MI (and specifically to evaluate the utility and validity of hs-cTn assessment) and to evaluate the utility of supporting evidence of myocardial ischemia.

Table 3. CTO-ARC Criteria for Procedural MI After CTO-PCI and CABG

Baseline biomarkers	Definition
Normal	CK-MB (within 48 h of the procedure): ≥10× URL OR ≥5× URL with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB OR Standard (non-hs) cTn (I or T)* (within 48 h of the procedure): ≥70× URL OR ≥35× URL with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB OR if hs-troponins must be used: hs-cTn (I or T) (within 48 h of the procedures): ≥70× URL with at least 1 of the following criteria: TIMI grade 0–1 flow in a main epicardial vessel or in a sidebranch >2.0 mm in diameter that had TIMI grade 2–3 flow before PCI† New pathological Q waves in ≥2 contiguous leads or new persistent LBBB New wall motion abnormality related to the procedure
Elevated but stable or falling	CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent preprocedure level
Elevated and not stable or falling	CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above Plus New ST-segment elevation or depression Plus Signs consistent with a clinically relevant MI (new onset or worsening heart failure or sustained hypotension)

ARC indicates Academic Research Consortium; CABG, coronary artery bypass graft; CK-MB, creatine kinase-MB; cTn, cardiac troponin; CTO, coronary chronic total occlusion; hs, high-sensitivity; LBBB, left bundle-branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; and URL, upper reference limit.

*The use of hs-troponin assays is strongly discouraged.

†For CTO-PCI, a side-branch occlusion as a factor contributing to a procedural MI definition would apply only to a branch that was patent before the CTO-PCI. Disruption of collateral flow may be considered equivalent to side-branch occlusion in this regard if the PCI procedure was unsuccessful (failure to restore antegrade flow). Persistent slow flow or no reflow must be differentiated from competitive flow from remaining collateral channels. TIMI grade 2 flow after CTO-PCI is considered a successful result (see success definition section) and thus should be differentiated from slow reflow with evidence of ongoing ischemia.

As noted in the ARC-2 publication, for a study intended for review by a regulatory authority, sponsors may propose a periprocedural MI definition for the primary analysis that is most appropriate for the trial design, taking into account the definition used in the control data sets in nonrandomized trials. The strengths and limitations of the various periprocedural MI definitions notwithstanding, CTO-ARC suggests that, when possible, additional analyses of periprocedural MI rates with alternative definitions be included

as secondary end points to assess the consistency of study outcomes.

Repeat Revascularization

CTO-ARC adopts the ARC-2 criteria for defining repeat revascularization, including target lesion revascularization (TLR) and TVR; however, several specific issues related to CTO-PCI deserve clarification.

TLR Versus TVR

CTO-ARC acknowledges the frequent challenge of attributing repeat revascularization to a specific target segment of the previously occluded vessel. Therefore, TVR (not TLR) is the preferred end point to assess patency.

Planned Repeat Revascularization

CTOs frequently occur in the context of multivessel disease, and their recanalization may necessitate longer procedures with higher doses of contrast and radiation. Thus, many patients with CTOs require staged procedures to facilitate complete revascularization. Treatment of non-CTO lesions is defined in Table 4 according to their timing relative to the index CTO procedure. As per the ARC-2 recommendations, such staged procedures that are prespecified are not considered MACEs.[32]

In addition, staged procedures may be required to recanalize the CTO lesion itself. Unique to CTO-PCI is the possibility of modifying the CTO (usually by balloon angioplasty) regardless of distal guide wire position. Previously called subintimal plaque modification or investment procedures, such procedures are now classified as CTO modification procedures, given the frequent uncertainty of the actual guide wire position. CTO-ARC defines CTO modification as intentional balloon dilatation (diameter ≥2.0 mm) of the entire CTO, including the proximal and distal caps and the CTO body. If stent placement is not performed, CTO modification procedures are considered unsuccessful procedures, regardless of whether a symptomatic benefit is realized. CTO modification procedures should be clearly documented in the case report form. A planned second CTO-PCI procedure may be attempted with or without a prior CTO modification procedure. CTO-ARC recognizes these second procedures as part of the initial therapeutic strategy (defined as a scheduled second procedure when complete CTO recanalization could not be achieved at the index procedure). If performed in a scheduled fashion within a study-defined time limit (eg, 3 months) and absent progressive symptoms, such second procedures are not considered an unplanned TVR event or MACE.

Table 4. Index Procedures and Planned Repeat Revascularizations

Classification	Definition
Index procedure	The first PCI procedure
Second index procedure	Planned second CTO-PCI after a first unsuccessful index procedure
Staged procedure	Planned procedure for the treatment of non-CTO lesions
Preindex	Before the CTO index procedure
Postindex	After the CTO index or second index procedure
CTO modification procedure*	Intentional modification of CTO plaque, including the proximal and distal caps and the CTO body, by a balloon sized ≥2.0 mm performed during the index procedure in the setting of unsuccessful CTO revascularization; this may or may not be followed by a second index procedure
Optimization procedure	Planned PCI of the target CTO vessel after a successful index procedure, usually for further optimization of the distal vessel (eg, balloon angioplasty and/or stenting) or the treated CTO lesion given positive remodeling after restoration of flow

CTO indicates coronary chronic total occlusion; and PCI, percutaneous coronary intervention.

*Formerly known as subintimal plaque modification or investment procedures.

After CTO-PCI, the distal vessel to an occlusion may be observed to be diffusely diseased or negatively remodeled and thus suboptimal for PCI. Such arterial segments may undergo significant positive remodeling with time after successful CTO recanalization and may warrant delayed treatment for complete revascularization. Stented segments may also increase in diameter early after the index CTO-PCI. Thus, an additional scheduled PCI may be needed to optimize the initial procedure.[5] If their performance is prespecified (eg, their intent declared at the completion of the first procedure) and completed within study-defined time windows, such planned optimization procedures are not considered adverse events. Conversely, if such procedures were driven by accelerating symptoms, they are considered TLR or TVR events.

If a third attempt is necessary to achieve successful CTO revascularization, given the burden to the patient, this procedure is considered a TVR event even if planned.

Unplanned Repeat Revascularization

Despite dual-catheter angiography, precise anatomic demarcation of CTO lesions may be uncertain. Furthermore, segments distal to the CTO are often diffusely diseased and may be treated by balloon angioplasty during the index procedure. In the past, TLR has been adjudicated in relation to an implanted stent– or balloon PCI–treated segment and TVR to the whole vessel and its branches targeted by the intervention. CTO-ARC adopts this convention with some modifications (Table 5).

CTO-PCI may involve instrumentation in areas that are not part of the initial target lesion, including contralateral arteries or distal territories during the retrograde approach, side-branch anchoring, and more. In

Table 5. Definitions Related to Clinically Driven Repeat Revascularization Procedures

Classification	Definition
Target lesion	Vessel segment intended to be treated. After CTO recanalization, the target lesion is assessed by an independent angiographic core laboratory, including 5-mm margins proximal and distal to the stented or ballooned segment.*
TLR	Repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.
Target vessel	The entire major intervened coronary vessel, including side branches.
TVR	Any repeat percutaneous intervention or surgical bypass of any new lesion for restenosis or other complication of the target vessel including the target lesion.
Target vessel non-TLR	Any repeat percutaneous intervention or surgical bypass of any new lesion (or other complication) in the target vessel excluding the target lesion.
CTO-related non-TVR*	Any repeat percutaneous intervention or surgical bypass of any new lesion in the nontarget vessel instrumented during the procedure (eg, proximal left anterior descending artery used as a retrograde route to revascularize a right coronary artery CTO) within 1 mo after the index (or second index) procedure if no intervention in this segment was performed during the index (or second index) procedure or indefinitely if any kind of intervention (ballooning, stenting, or scaffolding) was performed to treat any complication that occurred during the procedure.

CTO indicates coronary chronic total occlusion; TLR, target lesion revascularization; and TVR, target vessel revascularization.

*CTO-ARC modifications from the Academic Research Consortium-2 repeat revascularization definitions.

non–CTO-PCI, a branch occlusion and rescue as a result of main vessel stenting is considered part of the index procedure and not a MACE (unless criteria for a procedural MI are met). Similarly, additional interventions during the index procedure that are required in instrumented segments of the coronary tree remote from the target lesion (eg, left anterior descending artery used as a retrograde conduit to access the right coronary artery) is not considered adverse events at the index CTO-PCI. If any subsequent reintervention of such a segment is necessary during follow-up, however, this is considered a CTO-PCI–related non-TVR. In such cases, it is important to differentiate de novo disease in the remote vessel from a lesion that progressed secondary to the vessel instrumentation during the index CTO-PCI. CTO-ARC defines a 1-month time window to guide Clinical Events Committee adjudication in such cases. If a new lesion develops in an instrumented segment within 1 month, it is considered a CTO-PCI–related non-TVR; beyond 1 month, it is considered progressive de novo coronary artery disease.

Other recommendations for Clinical Events Committee adjudication, core laboratory analysis, hierarchical clinically driven revascularization assessment, and optimal and required data reporting are as per the ARC-2 recommendations.[32]

Device and Vessel Thrombosis

CTO-ARC recommends that ARC-2 criteria for device thrombosis be adopted but expanded for CTO-PCI to include symptomatic thrombosis of any area of the target vessel that was intervened on at the index procedure, not just a stented/scaffolded target lesion (Table XII in the Data Supplement). Consistent with considerations for TLR and TVR, symptomatic thrombosis of instrumented segments of the CTO vessel, donor arteries, and collaterals is also considered a CTO-PCI–related thrombosis if it occurs within 1 month of the index procedure.

The increasing use of CTO modification during CTO-PCI and more extensive vessel ballooning to promote runoff warrant stricter definitions of vessel reocclusion for CTO-PCI. CTO-ARC recommends only clinically driven vessel occlusions, as defined in ARC-2, be recorded as adverse events. For example, if a successfully recanalized CTO is noted to be reoccluded at follow-up angiography without any clinical sequelae (eg, MI, TVR, or death), it is not considered a MACE. Nonetheless, it is important to report non–MACE-related vessel occlusion.

Hospitalizations

Hospitalizations entail considerable clinical and economic consequences.[53] In CTO studies, hospitalizations may be considered an important end point, even without overt MACEs (eg, a patient with recurrent chest pain leading to hospitalization but who does not fit criteria for MI).

CTO-ARC defines hospitalization after a CTO-related procedure (PCI or CABG) as unplanned admission to an inpatient unit or hospital ward (or prolonged emergency department stay) for >24 hours. Hospitalizations planned for a staged procedure are excluded unless prompted ahead of schedule for progressive symptoms. It is recommended that the relatedness of unplanned hospitalizations be adjudicated to the index CTO-PCI. Hospitalizations may be further classified as cardiovascular or noncardiovascular in cause and as before or after 30 days of the procedure (Table XIII in the Data Supplement). Hospitalizations of undetermined cause or for which the predominant inciting event was uncertain are conservatively considered cardiovascular in type. In prospective registries, a final diagnosis compatible with an acute cardiac condition may be sufficient to classify the hospitalization as cardiovascular. Extended hospitalization for a complication of the index procedure is not counted as rehospitalization; a patient who leaves the hospital and is then readmitted counts as a subsequent hospitalization. It is recommended that a Clinical Events Committee adjudicate all hospitalization events.

Bleeding

Bleeding after surgical or percutaneous coronary procedures (especially non–access-site bleeding) has been strongly related to subsequent mortality.[54] The Bleeding Academic Research Consortium criteria have been proposed to define bleeding after coronary procedures.[55] In recognition that the optimal bleeding scale has not yet been identified, the CTO-ARC recommends the use of the Bleeding Academic Research Consortium classification as modified by the Mitral Valve Academic Research Consortium (Table XIV in the Data Supplement).[56] A classification for the high-bleeding-risk patient has also recently been proposed by the ARC group.[57] This classification may be used to assist evaluation of the risk-benefit tradeoffs of CTO-PCI in this high-risk population.

Access and Vascular Complications

CTO interventions may involve 1 or multiple arterial access sites, depending on the presence of previous CABG, number of grafts, how the CTO is collateralized, or the need for mechanical circulatory support. Moreover, CTO procedures often use larger sheaths and catheters compared with non–CTO-PCI procedures in order to accommodate the greater variety of devices needed.[58] Thus, vascular complications may be more frequent in CTO-PCI compared with non–CTO-PCI cases.

CTO-ARC recommends that the number of access sites, the location of those sites, and the largest introducer sheath used be recorded and that complications be tracked per access site and per patient but reported primarily on a per-patient basis. If a complication occurs in a staged procedure or during a second index procedure, per-patient reporting is recommended. Because of the higher number of access sites, it is important to document the degree of anticoagulation achieved, including the highest and lowest activated clotting time attained during the procedure.

For vascular complications that also result in a bleeding complication, events that meet CTO-ARC definitions are reported for both categories. Last, aortic damage may also occur during CTO-PCI (eg, from guide wire snaring, coronary ostium rotational atherectomy, electrocautery-assisted ostial reentry, ostial angioplasty, or guide catheter induced) and is categorized as a non–access-site vascular complication. CTO-ARC thus recommends that all vascular complications be recorded as either access site related or not access site related.

Acute Kidney Injury

Acute kidney injury (AKI) is an important complication that may occur in patients undergoing PCI and has been strongly related to subsequent mortality.[59,60] The pathogenesis of PCI-related AKI is multifactorial and may include contrast-induced nephropathy, atheroemboli, drug-induced mechanisms, and acute tubular necrosis resulting from renal hypoperfusion. In the absence of data on which AKI scale has the greatest prognostic utility, CTO-ARC recommends the adoption of Valve Academic Research Consortium-2/Mitral Valve Academic Research Consortium criteria for AKI in CTO trials and registries[56,61,62] (Table XV in the Data Supplement). Only the presence of AKI stage 2 or 3 (including new dialysis) is considered a major end point. AKI stage 1 should be tracked but not used to define the failure of the procedure. In addition to reporting the occurrence of AKI, it is important to document the need for renal replacement therapy (ultrafiltration or hemodialysis). For further details, see Acute Kidney Injury (page 12) and Table XV in the Data Supplement.

Radiation Exposure and Injury

The procedural complexity of CTO-PCI is associated with longer fluoroscopic times and greater radiation dose to both the patient and operator than with non–CTO-PCI.[63] CTO-ARC recognizes radiation injury as a serious adverse event and recommends that both cumulative air kerma (measured in Gy) and cumulative kerma-area product (measured in Gy·cm^2) are reported in CTO trials and registries (Table XVI in the Data Supplement). Tracking and reporting of acute and long-term clinical events related to radiation exposure and the number of procedures above 5 Gy (and/or 500 Gy·cm^2) are recommended. For further details, see Radiation Exposure and Injury (page 13) and Table XVII in the Data Supplement.

Perforations

Perforation is the most common complication of CTO-PCI, and its frequency increases with increasing lesion complexity.[26] Perforation can lead to tamponade, hemodynamic compromise, cardiac arrest, and death.[64] Perforations may require pericardiocentesis in case of tamponade. Depending on the perforation location, management may require prolonged balloon inflations, implantation of covered stents, embolization with coils, fat or thrombin, or emergency cardiac surgery. In post-CABG patients, perforation may lead to focal tamponade, cardiac chamber hematoma, or bleeding above the pericardial reflections into the chest or mediastinum.[65]

The modified Ellis classification of coronary perforations, originally published in 1994, divides perforation according to severity into 4 types (Table XVIII in the Data Supplement).[66] The Ellis classification has implications for management (Ellis type 3 perforations are more likely to require treatment) but does not describe the location of perforation. Relevant to CTO-PCI, there are 4 possible perforation locations: main vessel perforation,

distal branch perforation, septal collateral perforation, and epicardial collateral perforation (Table 6).[15,67]

CTO-ARC proposes a new coronary perforation classification in which each perforation is given 2 descriptors (Figure II in the Data Supplement): The first descriptor denotes the location of the perforation, and the second descriptor denotes its severity. Most coronary perforations are large vessel perforations.[67] If a perforation occurs, it is important to document the likely cause (eg, wiring the CTO segment, wiring a collateral channel, advancing the microcatheter into a collateral channel, ballooning the segment, placing the stent). CTO-ARC recommends recording management of the perforated segment (eg, prolonged balloon inflation, coil embolization, or covered stent) and of the extravasated blood (eg, pericardiocentesis or surgery).

Donor Vessel Complications

Dual injection is commonly used during CTO-PCI. Injection of the donor vessel allows visualization of the target vessel distal to the occlusion and improves the success and safety of the procedure.[68] In addition to the potential for retrograde vessel guide catheter–induced dissection and thrombosis, retrograde CTO-PCI involves advancing equipment (wires and microcatheters) through the donor vessel, which may lead to dissection or thrombosis, resulting in acute vessel closure, slow flow, and no reflow, with the potential for ischemia, infarction, and shock. CTO-ARC endorses the classification for donor vessel complications as outlined in the ARC-2 document (Table XIX in the Data Supplement).[32] There is, however, a nuance related to bypass graft patency in CTO-PCI. Loss of bypass graft patency can be considered only in grafts not related to the target vessel territory. For example, occlusion of a saphenous vein graft to the posterior descending artery used as retrograde route to revascularize a left anterior descending artery CTO is considered a donor vessel complication. However, if the target vessel is a right coronary artery CTO and the option is to revascularize the native coronary artery instead of the diseased graft, graft occlusion (intentional—by delivering coil, plug, and so forth—or unintentional) is not considered a donor vessel complication.

Table 6. Classification of Coronary Perforations According to Vessel of Origin

Location	Cause	Presentation/severity
Main vessel	Balloon inflation, stent deployment, device (such as guide wire or microcatheter) exit during coronary chronic total occlusion crossing attempts, use of atherectomy	Often severe (Ellis class 3) and immediately evident; can quickly lead to tamponade unless promptly treated
Distal branch	Guide wire (and sometimes microcatheter or other equipment) exit	May be subtle and not immediately recognized, potentially leading to delayed tamponade, often several hours later
Septal collateral	Septal collateral crossing attempts	Most septal collateral perforations do not lead to adverse outcomes
Epicardial collateral	Epicardial collateral crossing attempts	Can lead to tamponade

CTO-PCI CLINICAL TRIAL DESIGN PRINCIPLES

Although no single document can anticipate all the design goals and nuances of trials of CTO-PCI, CTO-ARC believes that thoughtful incorporation of the following principles is likely to result in studies with meaningful clinical outcomes that may meet regulatory standards and affect clinical practice.

Design Types and End Points for CTO Trials

CTO studies, whether randomized or registry/observational in design, can be categorized into 1 of 3 types: strategy trials (PCI versus optimal medical therapy [OMT] or CABG), evaluation of CTO recanalization devices, and assessment of adjunctive CTO-PCI drugs or device tools (eg, collagenase or intravascular imaging). CTO-PCI trial end points vary according to the study type and whether the study is intended to guide clinical practice, inform regulatory approval or labeling, or support reimbursement decisions through a health technology assessment.[69]

For the purpose of end point classification, we consider CTO strategy trials separately from CTO device/adjunct studies, which are grouped together. For each, we describe recommendations for primary effectiveness end point, secondary effectiveness end points, and safety end points.

For pivotal trials, CTO-ARC recommends a prespecified powered statistical hypothesis for the primary safety and effectiveness end points. Economic measures for all study types are considered separately. CTO-ARC end point recommendations for CTO-PCI trials are summarized in Table 7. Clinical trial quality is greatly enhanced by primary and major secondary end point adjudication by an independent Clinical Events Committee after review of original source documents and case report form data.

Strategy Trials

The recommended primary effectiveness end point for many CTO strategy studies is the angina frequency subscale of the SAQ (SAQ-AF) as a patient-related outcome measure.[28,31,70–72] Blinding of patients (when feasible) and end point assessors by use of a sham control (when feasible and appropriate) in a controlled randomized

Table 7. Recommendations for End Points in CTO-PCI Trials

Recommendations
Strategy trials (CTO-PCI vs OMT or CABG)
Primary effectiveness end point
SAQ-AF domain, or
All-cause mortality, or
Composite clinical end point: eg, death (all cause or cardiovascular) or MI (procedural and nonprocedural); clinically driven TVR or hospitalization for cardiovascular causes may also be considered as components*
Secondary effectiveness end points
PROM
Other SAQ domains
Physical limitation
Treatment satisfaction
QOL
Anginal stability
Dyspnea
Rose dyspnea scale
Depression
Example: PHQ-8 scale
Exercise duration
Goal after CTO-PCI: improvement of ≥60 s
Composite clinical end point as above (if PROM is the primary end point)
Safety end points
Clinical composite end points
Death or MI (noninferiority testing)
Short term (30 d): death, MI, stroke, vascular complications requiring surgical repair, AKI (or new dialysis), perforation requiring pericardiocentesis or surgery, stent thrombosis, donor vessel complications, BARC grade 3 or greater bleeding, ≥10-Gy radiation exposure, retained PCI equipment, or need for CABG
Trials assessing CTO-PCI device and adjunctive drugs and devices
Primary effectiveness end point
Technical/crossing success, device success, or procedural success
Secondary effectiveness end points
Tailored to each specific trial
PROM (especially relevant to support device reimbursement)
Exercise duration
Composite clinical end points
Safety end points
Same as for strategy trials

AF indicates angina frequency; AKI, acute kidney injury; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft surgery; CTO, coronary chronic total occlusion; CTO-ARC, Chronic Total Occlusion Academic Research Consortium; MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PHQ-8, 8-item Patient Health Questionnaire depression scale; PROM, patient-related outcome measure; QOL, quality of life; SAQ, Seattle Angina Questionnaire; and TVR, target vessel revascularization.

*SAQ may be included as a component in the composite clinical end point.

trial design is important to minimize bias. A clinically significant change in SAQ-AF score is 20 points,[70] underlying the need to restrict enrollment to patients with a SAQ-AF score ≤70 for potential detection of meaningful improvement. For clinical trials, an improvement in SAQ-AF score of ≥10 points also may be considered clinically relevant.[72]

The SAQ initial measurement before intervention on a stable maximally tolerated OMT ensures balanced allocation between strategies. Measurement of the long-term effect of CTO recanalization on SAQ-AF score (eg, at 1 year) is informative, as long as crossovers from the control group to PCI can be minimized or accounted for in the statistical analysis.[31,32]

Alternatively, either all-cause mortality alone or a clinical composite measure (eg, death, MI, clinically driven TVR with/without hospitalization for cardiovascular causes) may serve as a primary end point. The MI end point includes periprocedural MI (Table 3) to capture meaningful procedure-related complications. In some strategy trials, SAQ score changes may be included as a component in the composite end point. Of note, to date, only long-term mortality has consistently been reported to be reduced in patients with successful versus failed CTO-PCI.[73–75] Given the expected low death rate in the OMT control group (<5% at 4 years),[74,75] an adequately powered randomized trial with mortality alone as the primary end point would require several thousand patients to demonstrate CTO-PCI superiority.

Additional secondary effectiveness end points may include other SAQ subscale scores,[29,31,70] dyspnea quantified with the Rose dyspnea scale,[30,76,77] and exercise duration (total exercise time and duration to angina).[28,72,78] If a patient-related outcome measure is the primary end point, CTO-ARC recommends that a composite clinical end point be assessed as a secondary end point. Given the low frequency of most adverse events, one of several composite safety outcomes can also be prespecified as a primary safety end point. For further details, see Strategy Trials (page 14) in the Data Supplement.

Trials Assessing CTO-PCI Device and Adjunctive Drugs and Device Tools

The recommended primary effectiveness outcome for CTO device/adjunct trials is technical/crossing success, device success, or procedural success as previously defined. Secondary effectiveness end points can be tailored to each trial and may include the same patient-related outcome measures, exercise duration, and composite clinical end points recommended for strategy trials. The patient-related outcome measure end points are relevant especially if a health technology assessment is being considered to support reimbursement for the procedure and device. The same safety end points as for strategy trials may also be considered.

Economic Considerations

Economic evaluations to support reimbursement typically take the form of a cost-utility analysis whereby

the incremental cost of the intervention being evaluated is considered in the context of its incremental effectiveness compared with standard of care.[69] If a study is intended to inform reimbursement decisions, strong consideration should be given to the inclusion of a generic QOL instrument such as the EuroQol-5D[79] to allow utility and quality-adjusted life-year calculations.[80] Alternatively, cross-walk or mapping algorithms can be developed to calculate utility scores from scores on the SAQ domains.[81] CTO-PCI incurs a high upfront cost, which may be offset by future reductions in revascularization or medications. Therefore, a short time horizon for a cost-utility analysis such as 3 months may bias against the CTO intervention in some strategy trials because the cost offsets in the control arm would need time to accrue. To provide a lifetime time horizon, CTO-ARC recommends modeling to describe potential future effectiveness and cost differences between treatment groups, which, in turn, require assumptions of the sustainability of any benefit. For further details, see Economic Considerations (page 17) in the Data Supplement.

Control Group Therapies

The benefit-risk profile evaluation of a new device or strategy requires selection of an appropriate control group. For randomized CTO-PCI clinical trials, 3 different types of control groups may be considered: (1) OMT alone (with or without a sham control) when a surgical comparator is either not indicated (ie, is not standard of care) or is contraindicated because high surgical risk and no other comparator exists, (2) surgical therapy (plus OMT) when surgical therapy is standard of care and patients are acceptable surgical candidates, and (3) an active comparator device (plus OMT) if an alternative device is available and is considered a standard of care.

The safety and incremental effectiveness of procedural therapies are judged on background medical therapy. Maximally tolerated doses of OMT are indicated in all patients enrolled in CTO trials (ie, in both the control and treatment arms of randomized controlled trials), which includes appropriate antiplatelet therapy, statins, and antianginal therapy. Requiring maximally tolerated OMT in all patients minimizes the likelihood of uptitration of effective therapies, a particular risk in unblinded studies, which can create challenges in the interpretation of study results. For example, the benefit of transcatheter mitral valve repair demonstrated in the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) was greatly supported by trial design and execution elements that required medical therapy optimization before randomization, resulting in few major changes in background therapies in both treatment groups.[82]

In CTO studies, it is highly recommended to record the use and dose of all disease-modifying agents (eg, statins, platelet inhibitors) and antianginal therapies at baseline and at regular intervals during the course of a study. As in COAPT, CTO-ARC defines a major change in medication for each drug class as an increase in dose by >100% (including starting a new class of drug) or a decrease in dose >50% (including discontinuing a class of drug).[83]

For symptomatic patients enrolling in CTO trials, OMT includes maximally tolerated doses of at least a long-acting nitrate, β-blocker, and calcium channel blocker. Depending on the geography of enrollment and insurance issues, ranolazine, ivabradine, and trimetazidine may also be considered. In some trials, the optimization of OMT in individual patients (including drug class, dose, and patient compliance) before enrollment verified by a central eligibility committee can be considered to reduce bias associated with subjects changing their behavior under observation after enrollment (the Hawthorne effect). Intolerance to a drug or drug class or limitation in drug dosing should be based on objective clinical criteria, according to the known adverse effects of specific agents, and must be documented in the medical chart and a study eligibility case report form. If a patient presented to the eligibility committee has not been tried on maximal recommended doses of each of the 3 core antianginal drugs, deferring his or her enrollment might be considered until such a revision is made, a new stable baseline is reached (at least 8 weeks of the new regimen), and the patient is confirmed to still meet eligibility criteria (eg, still symptomatic). The patient may then be presented to the eligibility committee for reconsideration. Regardless of the magnitude of OMT use, before the patient is enrolled in the study, CTO-ARC recommends an agreement among the patient, referring physicians, and investigators that antianginal drugs will not be altered before the primary end point other than for patient safety or important side effects. After the primary end point is reached, a method may be introduced to the study protocol to reduce the number of antianginal drugs in the CTO-PCI arm to assess the benefits of revascularization on reducing the pharmaceutical burden.[84] Last, compliance with OMT is often challenging and is important to document at baseline and throughout the course of the study.

Aspirin and clopidogrel are the preferred dual antiplatelet agents after CTO-PCI in most patients, especially in sham control studies. Dual antiplatelet therapy is indicated for a minimum of 6 and 12 months in most patients enrolled with troponin-negative and -positive acute coronary syndromes, respectively. In this regard, most patients who undergo CTO-PCI have stable ischemic heart disease, although some may be enrolled after non–study-related treatment of a nontarget lesion in the setting of acute coronary syndrome (in whom

prasugrel or ticagrelor use is appropriate). Conversely, patients at high bleeding risk may be treated with more abbreviated antiplatelet regimens as allowed per protocol. If the patient requires oral anticoagulation (eg, for atrial fibrillation), monotherapy with clopidogrel may be used.[85]

Sham Control

For patients randomized to the control group in a CTO-PCI versus OMT trial, CTO-ARC recommends that a sham control procedure (when feasible) be performed to maintain blinding of the study patients and follow-up research personnel and healthcare providers. This procedure may consist of inserting an arterial sheath (radial access preferred to minimize risks) with or without angiography. Ethical concerns of performing angiography in the sham control arm are obviated if final angiographic eligibility of CTO anatomy must be confirmed during a diagnostic procedure, immediately after which randomization occurs. The patient blind can be maintained under standard sedation with the patient wearing music-playing headphones and the use of a script for ≈60 minutes that includes arterial sheath manipulation but no indwelling catheters or additional contrast administration. Although the operating physician and attendees in the cardiac catheterization laboratory cannot be blinded, use of a sham control minimizes bias by facilitating masking of study patients and the clinicians and investigators responsible for follow-up study assessments, therefore reducing Pygmalion effects (when the observer expectation may affect the end point), Hawthorne effects, and placebo and nocebo effects. It may also mitigate differences or variations of patient-reported health status in the control group, as well as patient effort and technician bias during the performance of exercise testing. A sham control design is especially important in trials in which the primary or major secondary end points relate to symptoms, QOL, or exercise performance, the perception or ascertainment of which may be strongly biased by the knowledge of whether a test therapy was or was not administered. A sham control will not be possible in all CTO-PCI trials, for example, if higher-risk surgical interventions are required. Whether the risks of the additional control group sham procedures are acceptable given the advantages that the study would gain by reducing bias should be discussed with and reviewed by regulatory bodies and institutional ethics committees. If a sham control design is used, sample size estimation should consider the possibility of symptom or exercise performance improvement in the control group over time, as well as greater treatment effects in more symptomatic patients.[78,86,87]

Crossovers

In CTO-PCI randomized controlled trials that assess revascularization (as opposed to just lesion crossing), CTO-ARC recommends avoiding the elective performance of PCI in the control arm (crossovers) until the primary end point has been reached. To minimize crossover, it is best to enroll only patients willing to be maintained on medical therapy during the primary end point assessment phase. Crossovers may be allowed by protocol, however, in patients presenting with rest angina with ECG changes, troponin-positive acute coronary syndrome, or hemodynamic instability. The reasons for crossover are described in case report forms, and whether crossover was appropriate can be adjudicated by the Clinical Events Committee.

Although the primary and major secondary end points of CTO-PCI randomized trials are most often analyzed by intention to treat (as described below), if crossover occurs, a last observation (before the crossover) carried forward analysis may be considered as a sensitivity assessment, along with per-protocol and as-treated analyses. In addition, a modified as-treated analysis can be performed including all patients treated with CTO-PCI before the end point assessment.

Inclusion and Exclusion Criteria

Recommended CTO-PCI study subjects are those with true CTOs supplying viable and ischemic myocardium. If the primary end point is QOL, it is expected that eligible patients should have reduced health status at baseline such as SAQ-AF scores ≤70 despite maximally tolerated OMT. Enrolling minimally symptomatic patients will preclude showing clinically significant improvements in health status outcomes. Alternatively, if the primary end point is longevity or MACEs, patients with any level of symptoms may be enrolled.

Published PCI recanalization success rates range from <40% to >95%.[30,73] To increase the likelihood of demonstrating clinical benefit within a randomized trial, a high (>90%) likelihood of CTO-PCI success should be anticipated, with a low (<3%) expected rate of major complications attributable to the target lesion and target vessel. Achieving these objectives requires balancing the complexity of the CTO lesion characteristics allowed (as determined by one of several risk scores) in relation to the expertise of the CTO operators participating in the trial. For example, if only expert CTO operators participate, few lesion restrictions may be necessary. As the level of operator expertise declines, it may be appropriate to reduce study lesion complexity. The sample size calculation will take into account the expected procedural failure rate, reflecting the balance of the anticipated CTO anatomic complexity (according to inclusion and exclusion criteria) and expertise levels of the participating operators.

Although each trial tailors the inclusion and exclusion criteria to the specific device and patient population

being studied, general recommendations for inclusion and exclusion criteria in CTO-PCI randomized trials are shown in Table 8.

Role of Noninvasive Assessment

Studies assessing functional end points ideally should enroll patients with reduced exercise capacity at baseline. It is recommended that global and regional left ventricular (LV) function (LV ejection fraction and regional all motion) be assessed before enrollment in all patients. In addition, for a randomized trial to maximize the likelihood of success, CTO-ARC recommends that CTO target vessels are in the distribution of viable and ischemic territory and that ischemia in the CTO territory is documented by noninvasive testing as a condition to enrollment. In studies assessing the impact of CTO-PCI on ischemia or LV ejection fraction, ischemia and LV function assessment by an independent core laboratory is recommended.[88] In addition, angina may be underrecognized in ≥40% of patients with coronary artery disease, with ischemia resulting in anginal equivalent symptoms such as dyspnea.[89] If ischemia in the CTO territory is uncertain (eg, as a result of multivessel disease), non-CTO lesions should be treated first and evidence for ischemia subsequently reassessed. Quantification of ischemia by an imaging method may demonstrate a reduction in the ischemic burden after CTO-PCI, which can be a clinically meaningful surrogate end point.

In a study evaluating changes in LV ejection fraction or regional wall motion, a myocardial viability assessment is recommended if akinetic or dyskinetic LV wall motion abnormalities related to the CTO artery are present. However, prior studies have reported conflicting data as to whether CTO-PCI improves global and regional LV function in viable versus nonviable segments.[90,91] Additional studies are warranted to determine whether myocardial viability is essential for CTO-PCI benefit. For studies with the hypothesis that CTO recanalization in patients with severe LV dysfunction will prolong life (eg, as was seen with surgical revascularization in the STICH trial [Surgical Treatment for Ischemic Heart Failure]),[92,93] demonstration of ischemia or viability may not be necessary.[94]

Extent of Disease

Ideally, patients undergoing intervention of CTO lesions only (ie, no PCI performed of nonoccluded segments) would be enrolled to isolate the effect of PCI recanalization of the coronary occlusion on outcomes. However, concomitant coronary artery disease is often present in patients with CTOs. Thus, as a practical consideration, patients with multivessel disease (with CTO and non-CTO lesions) may be enrolled in CTO-PCI trials, and stratification of randomization should be considered for this occurrence. However, it is recommended that non-CTO lesions in patients with multivessel disease be treated first (and successfully) at least 1 month before randomization, as was done in the EuroCTO trial.[27] This requirement excludes non–CTO-related short-term events (including periprocedural MI and stent thrombosis, most of which occur within 30 days) from diluting the differences between treatment groups. However, late adverse events arising from non–CTO-PCI–treated lesions, which are likely to occur with similar frequency

Table 8. Recommended Inclusion and Exclusion Criteria for CTO-PCI Randomized Trials

Recommended criteria
Inclusion criteria*
Age ≥18 y
Definite or probable CTO as per CTO-ARC definition
Documented viable and ischemic myocardium by noninvasive testing†
High likelihood (≥90%) of CTO-PCI success (balance between CTO lesion complexity and operator expertise)
Successful treatment of any non-CTO lesions at least 1 mo before randomization
CTO lesion location
Proximal and mid left anterior descending coronary artery, or
Proximal circumflex or large obtuse marginal branches, or
Proximal, mid or distal dominant right coronary artery
Specific inclusion criteria according to end point assessed
QOL: Include patients with reduced baseline health status (eg, SAQ-AF score ≤70) despite OMT
Survival/MACE: Include patients with any level of symptoms
Functional: Include patients with reduced exercise capacity
Change in ischemia or LV ejection fraction: Perform noninvasive testing and assess results by an independent core laboratory
Changes in LV ejection fraction or regional wall motion: assess myocardial viability testing if akinetic or dyskinetic LV wall motion abnormalities related to the CTO artery
Exclusion criteria
Life expectancy <1 y as a result of noncardiac conditions
Known cardiomyopathy or low LV ejection fraction (eg, <35%)‡
Multiple CTOs that require recanalization
Recent troponin-positive acute coronary syndrome (<3 mo)
Overt heart failure or cardiogenic shock
Estimated glomerular filtration rate ≤30mL/min
Any planned non–CTO-PCI after randomization before the primary end point is reached
Any condition making it unlikely the patient will be able to complete all protocol procedures (including compliance with OMT) and follow-up visits
Patient (or legal guardian) unable or unwilling to provide written informed consent before study enrollment; pregnant or patient of childbearing age unless a recent pregnancy test is negative

AF indicates angina frequency; CTO, coronary chronic total occlusion; CTO-ARC, Chronic Total Occlusion Academic Research Consortium; LV, left ventricular; MACE, major adverse cardiac events; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; QOL, quality of life; and SAQ, Seattle Angina Questionnaire.

*Any J-CTO score and previous failed CTO-PCI may be enrolled. Reference vessel diameter should not be used as an inclusion or exclusion criterion.

†May not be mandatory if the primary end point is mortality.

‡Exception: studies assessing whether CTO recanalization will prolong life in patients with severe LV dysfunction.

in both groups, will bias outcomes toward the null. This effect should be considered when powering the trial and may necessitate larger sample sizes. For this reason, it is prudent to exclude patients with very complex non-CTO lesions (eg, very long lesions, bifurcation lesions requiring 2 stents, calcified lesions requiring atherectomy). Therefore, complex higher-risk but indicated patients, especially those requiring LV support devices, deserve dedicated studies and probably should be excluded from CTO-specific studies, even when the target of treatment is ≥1 CTOs. Other patients who should generally be excluded from CTO-PCI trials include those with multiple CTOs, recent acute coronary syndrome (<3 months), overt heart failure or cardiogenic shock, estimated glomerular filtration rate ≤30 mL/min, and any non–CTO-PCI planned to be performed after randomization but before the primary end point is reached.

CTO-ARC also recommends that only CTOs of the proximal and mid left anterior descending coronary artery, proximal circumflex or large obtuse marginal branches, and proximal, mid, or distal dominant right coronary artery be included, regardless of the J-CTO score. Because the target vessel may have extensive disease or be negatively remodeled, reference vessel diameter is not useful as an inclusion or exclusion criterion. Patients with previous failed CTO-PCI may be included.

Follow-Up Duration

The follow-up period for CTO trials will depend on several factors, including symptom severity, disease burden, and principal study objectives. In highly symptomatic patients, a short-term primary end point focusing on QOL and functional outcomes may be preferred; 3 months may be an acceptable time point for the symptomatic and functional benefits of CTO recanalization to be assessed. However, as discussed, CTO-ARC recommends that blinding (if used) be maintained, crossovers be minimized, and follow-up be continued for at least 1 year to allow assessment of PCI effect durability and MACEs and to minimize placebo effects.

For trials with a primary mortality or MACE end point, we recommend at least 1 year of follow-up in all patients or alternatively variable follow-up ranging from a minimum of 6 months to ≥3 years. If the latter option is adopted, the trial may be powered for a total number of events, facilitating an adaptive design for trial size re-estimation partway through. However, a high crossover rate may be inevitable during long-term follow-up if highly symptomatic patients are enrolled, biasing the results toward the null hypothesis in an intent-to-treat analysis. Evaluating the effect of crossovers can be prespecified in the statistical analysis plan, and per-protocol and as-treated analyses are recommended. A long-term trial focusing on mortality or major adverse clinical cardiovascular events may be more likely to be successful and require fewer patients for adequate power if limited to enrollment of mildly symptomatic patients with CTO in whom the crossover rate from control to PCI may be held to <10%. For some trials (particularly those involving investigational devices), although the primary end point evaluation occurs at 1 year, subjects may be followed up longer (eg, for up to 5 years) to assess longer-term safety and effectiveness.

CONCLUSIONS

In contrast with nonocclusive coronary lesions, CTOs represent the most challenging lesion subset for PCI. Although no single definition is perfect for all therapies and situations, using uniform consensus definitions across studies provides greater consistency, is more informative than using varying ad hoc definitions, and can provide insights into comparative health outcomes. Clinical trial design for CTO therapies can be particularly challenging. CTO-ARC thus not only has provided uniform definitions for end points specific to CTO interventions but also recommends a consensus framework for the design of clinical trials and registries, including the procedural data collected during CTO-PCI. The present document is by its nature dynamic and will doubtless be updated in the future. Nonetheless, acknowledging that each study will entail its own nuanced considerations and adopting the principles advocated in this document as a template for clinical investigation of CTO therapeutics can allow sponsors and investigators to optimize clinical trials and enhance the validity and utility of their study results.

ARTICLE INFORMATION

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Supplemental Materials

Supplemental Text
Data Supplement Figures I–II
Data Supplement Tables I–XIX

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